

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wheeler et al. Art Unit : 1642  
Serial No. : 10/575,438 Examiner : Laura B. Goddard, Ph.D.  
Filed : April 11, 2006 Conf. No. : 4024  
Title : SYSTEM AND METHOD FOR THE TREATMENT OF BRAIN TUMORS

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

DECLARATION OF DR. JOHN S. YU UNDER 37 CFR § 1.132

I, John S. Yu, M.D., hereby declare as follows:

1. I am a physician and the Director of the Brain Tumor Center and Director, Surgical Neuro-Oncology in the Department of Neurosurgery at Cedars-Sinai Medical Center, the assignee of the above-referenced application. I am also Chief Scientific Officer and Chairman of the Board of ImmunoCellular Therapeutics, the licensee of the above-referenced application. My curriculum vitae is attached.

2. I have read the specification of the above-referenced application, including the last sentence of the brief description of Figure 2, which reads: "Survival of the vaccine group tended to be lower but was not statistically different than that of the vaccine+chemotherapy group ( $p=0.05$ , log-rank)." In my opinion, the last sentence of the brief description of Figure 2 is an obvious error. One skilled in the art could perform a statistical analysis of the data presented graphically in Figure 2 to determine that the  $P$  value was actually less than 0.05. A  $P$  value of less than 0.05 is generally considered to be statistically significant.

3. The same data presented in Figure 2 and described in the specification as "not statistically different" was also presented in the publication Wheeler et al., 2004, "Clinical responsiveness of glioblastoma multiforme to chemotherapy after vaccination," Clin. Cancer Res., 10:5316-26, of which I am a co-author with the inventors of the instant application and another researcher. A copy of this publication is attached to this declaration. Fig. 2 on page

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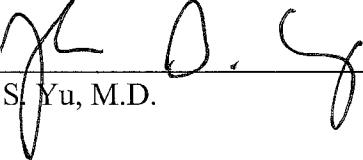
5321 of the Wheeler et al. publication presents the same data shown in Figure 2 of the present application. The legend for Fig. 2 of the Wheeler et al. publication reads:

Survival of vaccine + chemotherapy group was significantly greater relative to survival in the other two groups together ( $P = 0.048$ , log-rank test) . . . and greater than survival in the vaccine group alone ( $P = 0.048$ , log-rank test).

The result of the statistical analysis of the vaccine + chemotherapy group as compared to the vaccine group indicates that the difference in survival was statistically significant, with a  $P$  value of less than 0.05.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov. 13, 2009

  
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### **John S. Yu, MD**

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#### **Education:**

<b>Stanford University</b> , Stanford, California	
Biology and French Literature, with Distinction	1985
<b>Universite de Paris, Sorbonne</b> , Paris, France	
Biology and French Literature	1985
<b>Harvard University</b> , Cambridge, Massachusetts	
Genetics	1990
<b>Harvard Medical School</b> , Cambridge, Massachusetts	
Medical Degree	1990

#### **Post-Graduate Training:**

<b>Beth Israel Hospital</b> , Boston, Massachusetts	
Internship, General Surgery	1990-1991
<b>Massachusetts General Hospital</b> , Boston, Massachusetts	
Resident, Neurosurgery	1991-1997

#### **Academic Appointments:**

Instructor in Surgery	
Department of Neurological Surgery	
Harvard Medical School	
Boston, Massachusetts	1997

Assistant Clinical Professor  
Department of Neurological Surgery  
UCI Medical School  
Irvine, California 1997-2001

**Administrative Appointments:**

Assistant in Neurosurgery  
Neurosurgical Service  
Massachusetts General Hospital  
Boston, Massachusetts 1997

Co-Director, Comprehensive Brain Tumor Program  
Maxine Dunitz Neurosurgical Institute  
Department of Surgery  
Cedars-Sinai Medical Center  
Los Angeles, California 1997-Present

**Honors and Awards:**

Bachelor of Science Degree with Distinction and Honors	1985
Phi Beta Kappa Award of Honor in the Biological Sciences	1985
Preuss Resident Award, Joint Section on Tumors, AANS, and CNS	1995
Resident Award, American Academy of Neurological Surgery	1996
Joint Section on Tumors Young Investigator Award, American Association of Neurological Surgeons	
and Congress of Neurological Surgeons	2000
National Brain Tumor Foundation Grant, Joint Section on Tumors	2001
Marquis Who's Who in Medicine	2002-Present
Marquis Who's Who in Science and Engineering	2003-Present
America's Top Doctors (Castle-Connolly Medical, Ltd.)	2005
America's Top Cancer Specialists (Castle-Connolly Medical, Ltd.)	2005
Mahaley Clinical Research Award, Congress of Neurological Surgeons	2005

**Professional Societies and Memberships:**

American Association for the Advancement of Science  
American Association of Neurological Surgeons  
Joint Section on Tumors: American Association of Neurological Surgeons  
and Congress of Neurological Surgeons  
Society for Neuro-Oncology  
International Society for Cellular Therapy

**Certificates and Licensure:**

Massachusetts State Medical License	1990-1998
Diplomat, National Board of Medical Examiners	1990
California State Medical License	1997-Present
Diplomat, American Board of Neurological Surgery	2001

**University and Hospital Committees:**

Faculty Academic Advisory Council, Cedars-Sinai Medical Center	2002-Present
Quality Assurance Facilitator in Neurosurgery, Cedars-Sinai Medical Center	2002-Present
Cancer Committee, Cedars-Sinai Medical Center	2000-Present
Institutional Review Board, Cedars-Sinai Medical Center	2003

**National Service:**

Brain Tumor Progress Review Group Roundtable Participant, NCI/NINDS	2000
PPG Site Visit for Parent Subcommittee D (Clinical Research Studies), National Cancer Institute	2003
Ad Hoc Reviewer for Research Programs Review Branch, National Cancer Institute	2003
Congressionally Directed Medical Research Programs Peer Review Program Project Cluster Review for Parent Subcommittee C and D, National Cancer Institute	2003
	2004

**Editorial Boards:**

Editor: *Current Stem Cell Research and Therapy*  
Ad Hoc Reviewer: *Cancer Research, The Lancet, Clinical Cancer  
Research, Oncogene, Molecular Therapy, and Journal of Neuro-Oncology*

**Patents Awarded:**

A herpes simplex virus type 1 (HSV-1) derived vector for selectively inhibiting malignant cells (and methods for its use to treat cancers and express desired traits in malignant and non-malignant mammalian cells).

**(Provisional Patents):**

Intratumoral intracranial delivery of dendritic cells to brain tumors, with or without pretreatment of tumors with radiosurgery or thermal ablation (radiofrequency or microwave).

(A) In vitro differentiation of mammalian whole bone marrow into neural progenitor cells, glia, and neurons and (B) transplantation of autologous neural progenitor cells, neurons, or glia for the treatment of brain tumors, brain, spinal cord injuries, myelodysplasias, and neurodegenerative diseases.

Silencing interlukin-10 expression by small interference RNA (siRNA) to enhance Th1 response in human monocyte-derived dendritic cells.

A serum assay for malignant glioma using interleukin 13 receptor alpha.

**Research Experience:**

Department of Biology, Honors Research at Stanford University	1982-1984
Department of Molecular Biology, Genetech, Inc.	1984
Department of Immunology, Institut Pasteur (France)	1984-1985

**Grant Support Awarded:**

Fellow, Betty Lea Stone Fellowship, National Institute of Mental Health: Gene Transfer Strategies Based on a Chimeric EBV and Retrovirus Based Vector.	1986
Fellow, Neuroscience Fellowship, National Institute of Mental Health: The Genetic Etiology of Familial Multiple Sclerosis.	1988-1989
Fellow, Charles E. Culpeper Foundation Grant: GM-CSF Vaccination for Malignant Glioma.	1993-1995
Investigator, National Brain Tumor Foundation Award: Randomized Phase II Trial of Dendritic Cell Immunotherapy for Patients with Glioblastoma.	2001-2002
Principal Investigator, National Institutes of Health Research Grant: Active Immunotherapy for Glioblastoma.	2000-2005
Principal Investigator, National Institutes of Health Research Grant: A Novel Gene Therapy Approach for the Treatment of Glioblastoma.	2003-2005
Principal Investigator, National Institutes of Health Research Grant: Bone Marrow-Derived Neural Stem Cell Therapy for Glioma.	2004-2009

**Publications in Scientific Journals:**

1. Dautry F, Weil D, **Yu JS**, Dautry-Varsat A: Regulation of pim and myb mRNA accumulation by interleukin 2 and interleukin 3 in murine hematopoietic cell lines. J Biol Chem. 263:17615-17620, 1988.
2. **Yu JS**, Hayashi T, Seboun E, Sklar RM, Doolittle TH, Hauser SL: Fos RNA accumulation in multiple sclerosis white matter. J Neurol Sci. 103:209-215, 1991.
3. **Yu JS**, Moore MR, Kupsky WJ, Scott RM. Intracranial melanotic tumor of infancy: Two case reports. Surg Neurol. 37:123-129, 1992.
4. **Yu JS**, Pandey JP, Massacesi L, Lincoln R, Usuku K, Seboun E, Hauser SL: Segregation of immunoglobulin heavy chain constant region genes in multiple sclerosis sibling pairs. J Neuroimmunol. 42:113-116, 1993.
5. **Yu JS**, Wei MX, Chiocca EA, Martuza RL, Tepper RI. Treatment of glioma with genetically engineered interleukin-4 secreting cells. Cancer Res. 53:3125-3128, 1993.

6. Kramm CM, Sena-Esteves M, Barnett FH, Rainov NG, Schuback DE, **Yu JS**, Pechan PA, Paulus W, Chiocca EA, Breakefield XO: Gene therapy for brain tumors. *Brain Pathol.* 5:345-381, 1995.
7. **Yu JS**, Short MP, Schumacher J, Chapman PH, Harsh GR, IV: Intramedullary hemorrhage of spinal cord hemangioblastoma. Report of two cases. *J Neurosurg.* 81:639-40, 1996.
8. **Yu JS**, Sena-Esteves M, Paulus W, Breakefield XO, Reeves SA: Retroviral delivery and tetracycline-dependent expression of IL-1 $\beta$ -converting enzyme (ICE) in a rat glioma model provides controlled induction of apoptotic death in tumor cells. *Cancer Res.* 56:5423-5427, 1996.
9. Kim DH, Gutin PH, Noble LJ, Nathan D, Yu JS, Nockels RP: Treatment with genetically engineered fibroblasts producing NGF or BDNF can accelerate recovery from traumatic spinal cord injury. *Neuroreport.* 7:2221-2225, 1996.
10. **Yu JS**, Burwick JA, Dranoff G, Breakefield XO: Gene therapy for metastatic brain tumors by vaccination with granulocyte-macrophage colony-stimulating factor-transduced tumor cells. *Human Gene Therapy* 8(9), 1997.
11. Herrlinger U, Kramm CM, Johnston KM, Louis DN, Finkelstein D, Reznikoff G, Dranoff G, Breakefield XO, **Yu JS**: Vaccination for experimental gliomas using granulocyte-macrophage colony-stimulating factor-transduced glioma cells. *Cancer Gene Therapy* 4:345-352, 1997.
12. **Yu JS**: Gene therapy for brain tumors. *Drug News and Perspectives*. 10(6), 10:528-534, 1997.
13. Zeltzer PM, **Yu JS**, Black KL: Immunotherapy of malignant brain tumors in children and adults: From theoretical principles to clinical application. *Childs Nerv Syst.* 15:514-528, 1999.
14. **Yu JS**, Yong WH, Wilson D, Black KL: Glioblastoma induction after radiosurgery for meningioma. *Lancet* 356:1576-1577, 2000.
15. Schievink WS, Thompson RC, Levine S, **Yu JS**: Superficial temporal artery to middle cerebral artery bypass and external carotid reconstruction for carotid restenosis following angioplasty and stent placement. *Mayo Clin Proc.* 75:1087-1090, 2000.
16. **Yu JS**, Wheeler CJ, Zeltzer PM, Finger D, Lee PK, Pins R, Yong WH, Thompson RC, Riedinger M, Zhang W, Black KL: Vaccination of malignant glioma patients with peptide-pulsed dendritic cells elicits systemic cytotoxicity and intracranial T-cell infiltration. *Cancer Res.* 61:842-847, 2001.  
(Selected as cover illustration)
17. Samato K, Ehtesham M, Perng GC, Hashizume K, Wechsler SL, Nesburn AB, Black KL, **Yu JS**: A herpes simplex virus type 1 mutant deleted for gamma 34.5 and LAT kills glioma cells in vitro and is inhibited for in vivo reactivation. *Cancer Gene Therapy* 8(4):269-277, 2001.

18. Samato K, Ehtesham M, Perng GC, Hashizume K, Wechsler SL, Nesburn AB, Black KL, **Yu JS**: A herpes simplex virus type 1 mutant with gamma 34.5 and LAT deletions effectively oncolyses human U87 glioblastomas in nude mice. *Neurosurgery* 50(3):599-605, 2002.
19. Liu Y, Ehtesham M, Samoto K, Wheeler CJ, Thompson RC, Villarreal LP, Black KL, **Yu JS**. In situ adenoviral interleukin 12 gene transfer confers potent and long-lasting cytotoxic immunity in glioma. *Cancer Gene Ther*. 9:9-15, 2002.
20. Ehtesham M, Samoto K, Wheeler CJ, Thompson RC, Villarreal LP, Black KL, **Yu JS**: Treatment of intracranial glioma with *in situ* interferon-gamma and tumor necrosis factor alpha gene transfer. *Cancer Gene Therapy* 9(11):925-934, 2002.
21. Ehtesham M, Kabos P, Kabosova A, Neuman T, Black KL, **Yu JS**. The use of interleukin 12 secreting neural stem cells for the treatment of intracranial glioma. *Cancer Research* 62:5657-5663, 2002. (Selected as cover illustration)
22. Kabos P, Ehtesham M, Kabosova A, Black KL, **Yu JS**: Neural progenitors from adult bone marrow. *Experimental Neurology* 178(2):288-293, 2002. (Selected as cover illustration)
23. Ehtesham M, Kabos P, Gutierrez MAR, Chung NHC, Griffith TS, Black KL, **Yu JS**: Induction of glioblastoma apoptosis using neural stem cell mediated delivery of tumor necrosis factor-related apoptosis inducing ligand. *Cancer Research* 62(24):7170-7174, 2002.
24. Ehtesham M, Kabos P, Gutierrez MAR, Samoto K, Black KL, **Yu JS**: Intratumoral dendritic cell vaccination elicits potent tumoricidal immunity against malignant glioma. *Journal of Immunotherapy* 26:107-116, 2003.
25. Ehtesham M, Kabos P, Yong WH, Schievink WS, Black KL, **Yu JS**: Development of an intracranial ependymoma at the site of a pre-existing cavernous malformation. *Surgical Neurology* 60:80-2, 2003.
26. **Yu JS**, Lee PK, Ehtesham M, Samoto K, Black KL, Wheeler CJ: Intratumoral T-cell subsets and endothelial fas ligand expression in brain tumors. *J Neurooncol*. 64:55-61, 2003.
27. Liu G, Khong HT, Wheeler CJ, **Yu JS**, Black KL, Ying H: Molecular and functional analysis of tyrosine related protein (TRP)-2 as cytotoxic T lymphocyte target in malignant glioma. *J Immunother*. 26:301-12, 2003.
28. Kabos P, Ehtesham M, Black KL, **Yu JS**: Neural stem cells as delivery vehicles. *Expert Opin Biol Ther*. 3:759-70, 2003.
29. Wheeler CJ, Black KL, Liu G, Ying H, **Yu JS**, Zhang W, Lee PK: Thymic CD8+ T cell production strongly influences tumor antigen recognition and age-dependent glioma mortality. *J Immunology*. 171(9):4927-4933, 2003.
30. Ehtesham M, Kabos P, Black KL, **Yu JS**: Recent progress in immunotherapy for malignant glioma: Treatment strategies and results from clinical trials. *Cancer Control* 11(3):192-195, 2004.

31. Liu G, Ng H, Akasaki Y, Yuan X, Ehtesham M, Yin D, Black KL, **Yu JS**: Small interference RNA modulation of Interleukin 10 in human monocyte-derived dendritic cells enhances the Th1 response. *Eur J Immunology*. 34(6):1680-1687, 2004.
32. Ehtesham E, Kabos P, Chung NHC, Liu G, Akasaki Y, Black KL, **Yu JS**: Glioma tropic neural stem cells consist of astrocytic precursors and their migratory capacity is mediated by CXCR4. *Neoplasia* 6:287-293, 2004.
33. Kabos P, Matundan H, Zandian M, Bertolotto C, Robinson M, Davy BE, **Yu JS**, Krueger RC, Jr.: Neural Precursors express multiple chondroitin sulfate proteoglycans, including the lectican family. *Biochem Biophys Res Commun*. 318:955-63, 2004.
34. Liu G, **Yu JS**, Zeng G, Yin D, Xie D, Black KL, Ying H. AIM-2: A novel tumor antigen is expressed and presented by human glioma cells. *J Immunotherapy*. 27:220-226, 2004.
35. **Yu JS**, Liu G, Ying H, Yong WH, Black KL, Wheeler CJ: Vaccination with tumor lysate-pulsed dendritic cells elicits antigen specific cytotoxic T cells in patients with malignant glioma. *Cancer Res*. 64:4973-4979, 2004.
36. Liu G, Ying H, Zeng G, Wheeler CJ, Black KL, **Yu JS**: HER-2, gp100, and MAGE-1 are expressed in human glioblastoma and recognized by cytotoxic T cells. *Cancer Res*. 64:4980-4986, 2004.
37. Wheeler CJ, Das A, Liu G, **Yu JS**, Black KB: Clinical responsiveness of glioblastoma to chemotherapy after vaccination. *Clin Cancer Res*. 10(16):5316-5326, 2004.
38. Wheeler CJ, **Yu JS**, Black KL: Cellular immunity in the treatment of brain tumors. *Clin Neurosurg*. 51:132-139, 2004.
39. Akasaki C, Liu G, Chung NH, Ehtesham M, Black KL, **Yu JS**. Induction of a CD4<sup>+</sup> T regulatory type-1 response by cyclooxygenase-2 overexpressing glioma. *J Immunology*. 173(7):4352-4359, 2004.
40. Yuan X, Curtin J, Xiong Y, Liu G, Waschsmann-Hogiu S, Farkas DL, Black KL, **Yu JS**: Isolation of cancer stem cells from adult glioblastoma multiforme. *Oncogene* 23(58): 9392-9400, 2004.
41. Liu G, Akasaki Y, Khong HT, Wheeler CJ, Das A, Black KL, **Yu JS**: Cytotoxic T cell targeting of TRP-2 sensitizes human malignant glioma to chemotherapy. *Oncogene* 24(33):5226-5234, 2005.
42. Akasaki Y, Black KL, **Yu JS**: T cell immunity in patients with malignant glioma: Recent progress in dendritic cell-based immunotherapeutic approaches. *Front Biosci*. 10:2908-2921, 2005.
43. Akasaki Y, Black KL, **Yu JS**: Dendritic cell-based immunotherapy for malignant gliomas. *Expert Reviews Neurotherapeutics* 5(4):497-508, 2005.

44. **Yu JS**, Vilhauer J: Quality of life for patients with glioblastoma. Lancet Oncol. 6(12):913-914, 2005.
45. Akasaki Y, Liu G, Matundan HH, Ng H, Yuan X, Zeng Z, Black KL, **Yu JS**: A peroxisome proliferators-activated receptor-gamma (PPAR gamma) agonist, trogliazone, facilitates caspase-8 and caspase-9 activities by increasing the enzymatic activity of protein tyrosine phosphatase-1B on human glioma cells. J Biol Chem. Nov 30, 2005 (Epub. ahead of print).
46. Irvin DM, Yuan X, Zeng Z, Tunici P, **Yu JS**: Neural Stem Cells--A Promising Potential Therapy for Brain Tumors. Current Stem Cell Res & Ther., 1:79-84, 2006.
47. Yuan X, Hu J, Belladonna M, Black KL, **Yu JS**: IL-23 expressing bone marrow-derived neural stem-like cells exhibit antitumor activity against intracranial glioma. Cancer Res. (In press).
48. Tunici P, Liu G, Yuan X, Irvin DM, Zeng Z, Ng H, **Yu JS**: Brain tumor stem cells: New targets for clinical treatments? Neurosurgical Focus (In press).
49. Liu G, Black K, **Yu JS**: Sensitization of malignant glioma to chemotherapy through dendritic cell vaccination. Expert Review of Vaccines (In press).

**Book Chapters and Invited Articles:**

1. **Yu JS**, Harsh GR, IV, Breakefield XO: Basic concepts of gene therapy. Raffel C, Harsh GR, IV (eds): The Molecular Basis of Neurosurgical Disease Volume 8: Concepts in Neurosurgery. Williams and Wilkins, Maryland, 1996.
2. Ojemann RG and **Yu JS**: Anterior fossa tuberculum sella and olfactory groove meningiomas. Robertson JT, Coakham H (eds): Skull Base Surgery: Management, Complications, and Outcomes. Churchill Livingston, New York, 1998.
3. **Yu JS**, Carter BS, Harsh GR, IV: Gene therapy for metastases and carcinomatous meningitis. Maciunas RJ (ed): Advanced Techniques in Central Nervous System Metastases; Neurological Topics Series, American Association of Neurological Surgeons. Williams and Wilkins, Maryland, 1998.
4. **Yu JS**, Ehtesham M, Black KB: Immunotherapy for Malignant Gliomas. Black PM, Loeffler JS (eds): Cancer of the Nervous System, 2<sup>nd</sup> Edition. Lippincott, Pennsylvania, 2005.
5. **Yu JS**, Luptrawan A, Wallace RE, Hakimian B: Radiosurgery of intracranial lesions. Badie B (ed): Neurosurgical Operative Atlas. (In press) 2005.